ORAL PHARMACEUTICAL COMPOSITIONS OF CANDESARTAN CILEXETIL

Technical Field of the Invention

The present invention relates to pharmaceutical compositions of candesartan cilexetil and processes for their preparation.

Background of the Invention

Candesartan is a selective AT_1 subtype angiotensin II receptor antagonist. In the field of hypertension thereapy, angiotensin II receptor antagonists have attracted attention as effective agents for the treatment of hypertension in conjunction with angiotensin I converting enzyme (ACE) inhibitors. Candesartan cilexetil is a prodrug that is hydrolyzed in the gastrointestinal tract during absorption to form candesartan. It falls in the class of benzimidazole -7- carboxylic acids and their derivatives. These agents exhibit a stronger and more effective hypotensive action when compared to other classes of ACE inhibitors. They also are less likely to cause coughing as a side effect. Candesartan cilexetil is stable against temperature, moisture and light when it is alone in the solid state. However, when it is prepared into tablets and incorporated in with other ingredients, it has been observed that the active ingredient degrades over time.

U.S. Patent No. 5,534,534 discloses that the reduction in the content of the candesartan cilexetil with the lapse of time in pharmaceutical compositions can be reduced by incorporating oily substances having a low melting point in these compositions. According to the patent, the oily substance is incorporated with the active component to form a stable composition that suppresses the decomposition over time that is caused by compression. The resulting composition is described as being stable with minimal crystalline disorder.

The stability of pharmaceutical compositions of candesartan cilexetil can also be correlated to various degradation products, such as desethyl candesartan and other related substances. The levels of these related substances serve as a measure of the composition's overall stability.

Summary of the Invention

In one general aspect there is provided a pharmaceutical composition that includes a candesartan cilexetil and one or more fatty substances being present at a concentration of about 0.5% to about 10% w/w.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the fatty substances may be lipids and phospholipids. The lipids may be fatty acids and fatty acid esters. The fatty acids may be one or more of lauric acid, myristic acid, stearic acid, palmitoleic acid, oleic acid, capric acid, caprylic acid, oleic acid, linoleic acid, arachidonic acid and mixtures thereof. The fatty acid esters may be one or more of glycerol stearate, glycerol palmitate, glyceryl caprate, glyceryl caprylate, glyceryl caprylate/ caprate, glycerol oleate, glycerol linoleate, glyceryl lauropalmitooleate and mixtures thereof.

The phospholipids may be phosphoglycerides and sphingolipids. The phosphoglycerides may be one or more of lecithin, cephalin, soyalecithin, egglecithin, phosphatidylserine, phosphatidyl-inositol and mixtures thereof.

The candesartan cilexetil may be present in the pharmaceutical composition in a range of about 2% to about 35% w/w. The composition may further include one or more pharmaceutically acceptable excipients. The one or more pharmaceutically acceptable excipients may be one or more of fillers, binders, disintegrants, lubricants, coloring and flavoring agents. The pharmaceutical composition may be in the form of a tablet or a capsule and the tablet may further include a coating, the coating including one or more functional and/or non-functional layers.

In another general aspect there is provided a process for the preparation of a pharmaceutical composition. The process includes dispersing candesartan cilexetil and one or more fatty substances at a concentration of about 0.5% to about 10%w/w in a binder solution to form a dispersion; granulating the dispersion with one or more fillers and the one or more disintegrants to form granules; and drying, sizing, lubricating and compressing the granules into tablets.

Embodiments of the process may include one or more of the following features or those described above. For example, the dispersion may further include one or more fillers. The dispersion also may further include one or more disintegrants. The granulation may be wet granulation and/or dry granulation.

In another general aspect there is provided a method for the treatment of hypertension in a patient in need thereof. The method includes administering a pharmaceutical composition that includes candesartan cilexetil and one or more fatty substances at a concentration of about 0.5% to about 10% w/w.

Embodiments of the method treatment may include one or more of the following features or those described above. For example, the fatty substances may include lipids and phospholipids. The candesartan cilexetil may be present in a range of about 2% to about 35% w/w.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The present inventors have now surprising found that the use of fatty substances at a concentration of about 0.5% to about 10% w/w of the total composition results in stable pharmaceutical compositions of candesartan cilexetil. These pharmaceutical formulations have low levels of impurities, in particular desethyl candesartan and other related substances. Further, the present invention provides an economical method of stabilizing pharmaceutical compositions of candesartan cilexetil and enhances the shelf life of the product.

The term candesartan cilexetil as used herein refers to a prodrug that is hydrolyzed to form candesartan during its absorption from the gastrointestinal tract. Candesartan cilexetil may be present at a concentration range of about 2% to about 35% w/w, and particularly from about 3% to about 30% w/w, based on the total weight of the composition.

The pharmaceutical composition of candesartan may also include one or more other active agents. Suitable other active agents include one or more diuretics, sympathoplegic agents, vasodilators, ACE inhibitors and angiotensin receptor antagonists. In each case, the other active agent may be in the free form or in the form of a pharmaceutically acceptable salt.

The term 'stabilized pharmaceutical composition' refers to a composition capable of maintaining excellent stability with respect to the levels of impurities, especially desethyl candesartan and other total related substances.

Suitable stabilizing agents include one or more fatty substances. Suitable fatty substances include one or more of lipids, phospholipids and mixtures thereof. Lipids include fatty acids and fatty acid esters. The one or more fatty substance may be present in a concentration of about 0.5% to about 10% w/w, particularly from about 1% to about 5% w/w, based on the total weight of the composition.

Suitable fatty acids include one or more of lauric acid, myristic acid, stearic acid, palmitoleic acid, oleic acid, capric acid, caprylic acid, oleic acid, linoleic acid, arachidonic acid and mixtures thereof. Suitable fatty acid esters include one or more of glycerol stearate, glycerol palmitate, glyceryl caprate, glyceryl caprylate, glyceryl caprylate/caprate, glycerol oleate, glycerol linoleate, glyceryl lauropalmitooleate and mixtures thereof.

Suitable phospholipids include phosphoglycerides, sphingolipids and mixtures thereof. Suitabe phosphoglycerides include one or more of lecithin, cephalin, soyalecithin, egglecithin , phosphatidylserine, phosphatidyl-inositol and mixtures thereof.

These above stabilizing agents may be used alone or in a mixture of two or more of these agents.

As described in more detail below, the compositions described herein may also include one or more pharmaceutically acceptable excipients. The pharmaceutical compositions may be prepared by processes known in the prior art, such as wet granulation, dry granulation and direct compression. The pharmaceutical compositions may be in the form of tablets or capsules.

Also provided are processes for the preparation of pharmaceutical compositions of candesartan cilexetil. The process includes dispersing candesartan cilexetil and one or more fatty substances in the binder solution to form a dispersion. The dispersion is then granulated with one or more fillers and one or more disintegrants to form granules. The granules are then dried, sized, lubricated and compressed into tablets.

The pharmaceutical compositions of candesartan cilexetil may also be prepared by dispersing candesartan cilexetil, one or more fatty substances and one or more fillers in binder solution to form a dispersion. The dispersion is then granulated with one or more fillers and one or more disintegrants. The granules are then dried, sized, lubricated and compressed into tablets.

Pharmaceutical compositions of candesartan cilexetil may also may be prepared by dispersing candesartan cilexetil, one or more fatty substances and one or more distintegrants in a binder solution to form a dispersion. The dispersion then is granulated with one or more disintegrants and one or more fillers. The granules then are dried, sized, lubricated, and compressed into tablets.

The term 'other pharmaceutically acceptable excipient' refers to ingredients of the composition, excluding the active drug substance. Suitable pharmaceutically acceptable excipients include one or more of fillers, binders, disintegrants, lubricants, glidants, colors and mixtures thereof.

Suitable fillers include one or more of corn starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silicified microcrystalline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, starch pregelatinized and mixtures thereof.

Suitable binders include one or more of methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol and mixtures thereof.

Suitable disintegrants include one or more of calcium carboxymethyl cellulose, colloidal silicon dioxide, starch, croscarmellose sodium, crospovidone, sodium starch glycolate and mixtures thereof.

Suitable lubricants and glidants include one or more of colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and mixtures thereof.

Suitable coloring agents include any FDA approved colors for oral use.

The tablets may also be coated with one or more additional layers of film forming agents and/or pharmaceutically acceptable excipients.

The coating layers over the tablet may be applied as a solution/dispersion of the coating ingredients using any conventional technique known in the prior art. Such processes include spray coating in a conventional coating pan or fluidized bed processor and dip coating. Suitable solvents used for preparing a solution/dispersion of the coating ingredients include one or more of methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.

Suitable film forming agents include one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimelliatate, cellulose acetate phthalate; waxes, such as polyethylene glycol; methacrylic acid polymers, such as Eudragit ® RL and RS; and mixture thereof. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry® may also be used for coating.

The following examples are illustrative of the invention, and are not to be construed as limiting the invention.

EXAMPLE 1

Ingredient	Example 1 (wt/tablet) mg
Intragranular ingredients	
Candesartan cilexetil	32.12
Glyceryl caprate	8.00
Lactose monohydrate	265.88
Starch	67.00
Hydroxypropyl cellulose	12.00
Calcium carboxymethyl cellulose	6.50
Purified water	q.s
Extragranular ingredients	
Calcium carboxymethyl cellulose	6.50
Magnesium stearate	2.00

PROCEDURE:

1. Candesartan cilexetil and glyceryl caprate were dispersed in a solution of hydroxypropyl cellulose in water.

2. Lactose, starch and a part of the calcium carboxymethyl cellulose were mixed in a high shear mixer and granulated with the dispersion of Step 1.

3. The wet granules were then dried in a fluid bed drier, passed through a screen and then sized.

4. The remaining part of the calcium carboxymethyl cellulose was passed through a screen and blended with the granules of step 3.

5. The magnesium stearate was then passed through a screen, blended with the blend of step 4 and the total mixture compressed into tablets.

EXAMPLE 2

Ingredient	**Example 2 (wt/tablet) mg**
Intragranular ingredients	
Candesartan cilexetil	32.12
Glyceryl caprylate	8.00
Lactose monohydrate	250.88
Microcrystalline cellulose	67.00
Hydroxypropyl cellulose	12.00
Calcium carboxymethyl cellulose	10.00
Colloidal silicon dioxide	8.00
Purified Water	q.s
Extragranular ingredients	
Calcium carboxymethyl cellulose	10.00
Magnesium stearate	2.00

PROCEDURE:

1. Candesartan cilexetil, glyceryl caprylate and a part of the lactose were dispersed in a solution of hydroxypropyl cellulose in water.

2. The remaining part of lactose, microcrystalline cellulose, a part of calcium carboxymethyl cellulose and colloidal silicon dioxide were mixed in a high shear mixer and granulated with the dispersion of Step 1.

3. The wet granules were dried in a fluid bed drier, passed through a screen and then sized.

4. The remaining quantity of calcium carboxymethyl cellulose was passed through a screen and blended with the granules of step 3.

5. The magnesium stearate then was passed through a screen, blended with the blend of step 4 and the total mixture compressed into tablets.

EXAMPLE 3

Ingredient	Example 3 (wt/tablet) mg
Intragranular ingredients	
Candesartan cilexetil	32.12
Soyalecithin	8.00
Lactose monohydrate	250.88
Starch	67.00
Hydroxypropyl cellulose	12.00
Calcium carboxymethyl cellulose	10.0
Colloidal silicon dioxide	8.0
Purified Water	q.s
Extragranular ingredients	
Calcium carboxymethyl cellulose	10.00
Magnesium stearate	2.00

PROCEDURE:

1. Candesartan cilexetil, soyalecithin and a part of the calcium carboxymethyl cellulose were dispersed in a solution of hydroxypropyl cellulose in water.

2. The starch, lactose and colloidal silicon dioxide were mixed in a high shear mixer and granulated with the dispersion of Step 1.

3. The wet granules were dried in a fluid bed drier, passed through a screen and then sized.

4. The remaining part of the calcium carboxymethyl cellulose was passed through a screen and blended with the granules of step 3.

5. The magnesium stearate was then passed through a screen, blended with the blend of step 4 and the total mixture compressed into tablets.

The one or more fatty substances show a stabilizing effect on candesartan cilexetil. Table 1 compares stability data at various intervals (40°C/75%RH) with reference to the amount of desethyl candesartan and total related substances found.

TABLE 1

	Batch without stabilizer		Batch with glyceryl caprate as stabilizer (Example 1)		Batch with soyalecithin as stabilizer (Example 3)	
	Initial	1M	Initial	1M	Initial	1M
Desethyl Candesartan (% w/w)	0.363	0.845	0.061	0.153	0.122	0.251
Total RS (% w/w)	1.342	2.524	0.821	1.000	0.861	1.334

Table 1 indicates that the use of one or more fatty substances stabilizes the candesartan cilexetil compositions.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.